

University of Groningen

Ethnic differences in atrial fibrillation among patients with heart failure in Asia

ASIAN-HF Investigators; Tan, Eugene S. J.; Goh, Vera; Santema, Bernadet T.; Tay, Wan Ting; Teng, Tiew-Hwa Katherine; Yap, Jonathan; Tromp, Jasper; Hung, Chung-Lieh; Chopra, Vijay

Published in:
ESC Heart Failure

DOI:
[10.1002/ehf2.12696](https://doi.org/10.1002/ehf2.12696)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

ASIAN-HF Investigators, Tan, E. S. J., Goh, V., Santema, B. T., Tay, W. T., Teng, T-H. K., Yap, J., Tromp, J., Hung, C-L., Chopra, V., Anand, I., MacDonald, M. R., Ling, L. H., Van Gelder, I. C., Rienstra, M., Voors, A. A., Richards, A. M., & Lam, C. S. P. (2020). Ethnic differences in atrial fibrillation among patients with heart failure in Asia. *ESC Heart Failure*, 7(4), 1419-1429. <https://doi.org/10.1002/ehf2.12696>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).



The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Ethnic differences in atrial fibrillation among patients with heart failure in Asia

Eugene S.J. Tan¹ , Vera Goh², Bernadet T. Santema³, Wan Ting Tay⁴, Tiew-Hwa Katherine Teng^{4,5}, Jonathan Yap⁴, Jasper Tromp^{3,4}, Chung-Lieh Hung⁶, Vijay Chopra⁷, Inder Anand⁸, Michael R. MacDonald⁹, Lieng Hsi Ling¹, ASIAN-HF investigators, Isabelle C. Van Gelder³, Michiel Rienstra³, Adriaan A. Voors³, A. Mark Richards^{1,10,11} and Carolyn S.P. Lam^{3,4,12*} 

¹Department of Cardiology, National University Heart Centre Singapore, Singapore; ²Department of Internal Medicine, Singapore General Hospital, Bukit Merah, Singapore; ³Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands; ⁴Department of Cardiology, National Heart Centre Singapore, Singapore; ⁵School of Population and Global Health, University of Western Australia, Australia; ⁶Department of Cardiology, Mackay Memorial Hospital, Taipei, Taiwan; ⁷Department of Cardiology, Max Super Speciality Hospital; ⁸Department of Cardiology, Veterans Affairs Medical Center, Minneapolis, MN, USA; ⁹Department of Cardiology, Changi General Hospital, Singapore; ¹⁰Cardiovascular Research Institute, National University Heart Centre Singapore, Singapore; ¹¹Department of Cardiology, University of Otago, Dunedin, New Zealand; ¹²Department of Cardiovascular Sciences Academic Clinical Program, Duke—National University of Singapore Medical School, Singapore

Abstract

Aims We aimed to characterize ethnic differences in prevalence, clinical correlates, and outcomes of atrial fibrillation (AF) in heart failure (HF) with preserved and reduced ejection fraction (HFpEF and HFrEF) across Asia.

Methods and results Among 5504 patients with HF prospectively recruited across 11 Asian regions using identical protocols in the Asian Sudden Cardiac Death in Heart Failure study (mean age 61 ± 13 years, 27% women, 83% HFrEF), 1383 (25%) had AF defined as a history of AF and/or AF/flutter on baseline electrocardiogram. Clinical correlates of AF were similar across ethnicities and included older age, prior stroke, higher NT-proBNP, and larger left atria. Diabetes was associated with lower odds of AF in HFrEF [adjusted odds ratio (AOR) 0.79, 95% CI 0.66–0.95] and HFpEF (AOR 0.58, 95% CI 0.39–0.84) regardless of ethnicity. Compared with Chinese ethnicity, Japanese/Koreans had higher odds of AF in HFrEF (AOR 1.76, 95% CI 1.40–2.21), while Indians had lower odds in HFrEF (AOR 0.18, 95% CI 0.13–0.24) and HFpEF (AOR 0.28, 95% CI 0.16–0.49) even after adjusting for clinical covariates. Interaction between ethnicity and region was observed among Indians, with Southeast Asian Indians having higher odds of AF (AOR 3.01, 95% CI 1.60–5.67) compared with South Asian Indians. AF was associated with poorer quality of life and increased risk of 1 year all-cause mortality or HF hospitalisation (adjusted hazard ratio 1.39, 95% CI 1.18–1.63) regardless of ethnicity.

Conclusions Among patients with HF across Asia, clinical correlates and adverse outcomes associated with AF are similar across ethnicities; however, there are striking ethnic variations in the prevalence of AF that are not accounted for by known risk factors.

Keywords Atrial fibrillation; Heart failure; Diabetes

Received: 20 January 2020; Accepted: 12 March 2020

*Correspondence to: Carolyn SP Lam, MBBS, PhD, 5 Hospital Drive, Singapore 169609. Tel: +65 6704 2247; Fax: +65 6844 9056. Email: carolyn.lam@duke-nus.edu.sg
See Appendix 1 for list of ASIAN-HF investigators.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in heart failure (HF) and is associated with an increased risk of stroke, HF hospitalisation and mortality.^{1,2} Beyond traditional risk factors, there is growing evidence of ethnic influences on the prevalence of AF in the context of HF.^{3–7} A large US

registry reported a higher prevalence of AF among white HF patients compared with blacks, Hispanics, and Asians³; while a prospective Asia Pacific study showed a distinctly lower prevalence of AF among Singaporean–Asian compared with New Zealand European HF patients.⁵ The ethnic differences in AF prevalence in HF, while striking, remain poorly understood.

Asia is geographically vast, with significant heterogeneity among patients with HF not only by region but also by ethnicity.⁸ It is unknown if ethnic differences in AF prevalence and clinical correlates within Asia are present. We aimed to characterize ethnic differences in prevalence, clinical correlates, and outcomes of AF in HF with preserved and reduced ejection fraction (HFpEF and HFrEF) across Asia.

Methods

Study population

Participants were identified from the Asian Sudden Cardiac Death in HF (ASIAN-HF) registry (ClinicalTrials.gov Identifier: NCT01633398).⁸ In brief, ASIAN-HF is a prospective, observational, multinational registry of Asian patients with symptomatic HF. Consecutive patients were screened in 46 medical centres across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand) managing both acute and chronic HF. Patients were >18 years and provided written informed consent. Exclusion criteria have previously been described.⁸ The study complied with the Declaration of Helsinki, and ethics approvals were obtained at all sites. All patients enrolled in ASIAN-HF had a validated clinical diagnosis of HF by independent site investigators (based on symptoms, signs, and clinical decompensation within 6 months). They were categorized as HFrEF and HFpEF based on left ventricular ejection fraction <40% and ≥50%, respectively. In addition, 99.5% of HFpEF patients had echocardiographic evidence for diastolic dysfunction [$E/e' \geq 13$, e' medial/lateral <9 ms, left atrial (LA) enlargement, or left ventricular (LV) hypertrophy].⁹

Recruitment of patients in ASIAN-HF was in two phases, through investigation sites which covered a broad spectrum of medical, cardiology, and HF specialty units, admitting patients with acute HF and conducting outpatient follow-up of patients with chronic HF. HFrEF patients were recruited between October 2012 and December 2015; patients with HFpEF were enrolled between September 2013 and December 2017.

Data collection included patient demographics, clinical symptoms, co-morbidities, and medications. Standard 12-lead electrocardiogram (ECG) and transthoracic echocardiography were performed in all patients at baseline. Each centre performed transthoracic echocardiography exams according to internationally accepted guidelines. These assessments included measurements of LV systolic (EF) and diastolic function (E/e'), as well as LA and LV dimension and volumetric quantifications. The Cardiovascular Imaging Core Laboratory of the National University Health System, Singapore, provided oversight and imaging protocol guidelines for quality assurance of echocardiograms. Quality of life

(QoL) assessments were based on the Kansas City Cardiomyopathy Questionnaire (KCCQ),¹⁰ made available in local languages in all centres. Quintiles Outcomes, the contract research organisation appointed by the ASIAN-HF academic executive committee, handled all registry operations and data management. ASIAN-HF was an investigator-led study.

Study definitions

Atrial fibrillation was defined as a documented history of AF based on medical records and/or presence of AF/atrial flutter on baseline 12-lead ECG. Patients with a history of AF and AF on baseline ECG were classified as 'persistent AF'; history of AF without AF on baseline ECG classified as 'paroxysmal AF'; AF on baseline ECG without history of AF classified as 'new-onset AF'; sinus rhythm on baseline ECG without history of AF defined as 'sinus rhythm'. Only 'AF' and 'sinus rhythm' were included in this study; other ECG rhythms were excluded. Diabetes was defined as presence of a prior diagnosis (fasting plasma glucose ≥ 7 mmol/L, random plasma glucose ≥ 11.1 mmol/L, or HbA1C $\geq 6.5\%$) and/or treatment with anti-diabetic medications. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73m².

Geographical blocs were defined in accordance with the United Nations Statistics Division subregion classification: Northeast Asia (South Korea, Japan, Taiwan, Hong Kong, and China), South Asia (India), and Southeast Asia (Thailand, Malaysia, Philippines, Indonesia, and Singapore). Ethnicity was defined as self-reported Chinese, Malay, Indian, Japanese/Korean, and indigenous Southeast Asians (others).

Patients were routinely followed up every 6 months at each participating site. The primary outcome of this study is composite all-cause mortality or HF hospitalisation within 1 year. Follow-up data were available in 4973 (90%) patients at 1 year (10% lost to follow-up). An independent outcomes committee adjudicated all outcome events.

Statistical analysis

Baseline characteristics were reported as percentages (%) for categorical variables and mean \pm standard deviation or median (lower quartile, upper quartile) for continuous variables. Differences in baseline characteristics were assessed with independent *t*-test (continuous), χ^2 test (categorical), or Mann-Whitney *U* test (non-parametric). Univariable logistic regression was performed for each clinical correlate in its association with AF in each HF type and tested for interaction by ethnicity. The association of other ethnicities with AF compared with Chinese was examined in multivariable analyses adjusting for demographics, clinical correlates, and medications. Chinese and Indians were further stratified to assess

the association of geography with AF. Because of limited availability of LA volume index (LAVI) data, multivariable analyses were repeated with the inclusion of LAVI as sensitivity analyses. To further investigate the effects of diabetes, the association of diabetic medications with AF was evaluated with multivariable analyses. Interactions between diabetes with body mass index (BMI) and LAVI were investigated, and stratification performed if present to evaluate the association of diabetes with AF in the subgroups. Mean KCCQ scores in each domain were adjusted for demographics and clinical factors. The association of AF with primary outcome was performed by multivariable Cox regression analysis in the whole cohort of HF, with testing for interaction by ethnicity and HF type. Kaplan–Meier survival curves of subgroups by ethnicity with and without AF were performed and

compared by log-rank test. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS Version 21 (IBM Corporation, NY) or Stata/MP 13.0 (StataCorp LP).

Results

Among 5504 patients from the ASIAN-HF registry included in this study [mean age 61 ± 13 years, 27% women, BMI 25 ± 5 kg/m², 4541 (83%) HFrEF, 963 (17%) HFpEF], 1383 (25%) had AF (53% persistent AF, 34% paroxysmal AF, 8% new-onset AF, 5% history of AF but missing ECG data). The prevalence of AF was significantly lower in HFrEF (22%) than

Table 1 Comparison of baseline characteristics by AF status in HFrEF and HFpEF

	HFrEF			HFpEF		
	Sinus rhythm	AF	<i>P</i> value	Sinus rhythm	AF	<i>P</i> value
<i>n</i> (%)	3523 (78)	1018 (22)		598 (62)	365 (38)	
Characteristics						
Age, years	58 ± 13	65 ± 12	<0.001	66 ± 13	73 ± 10	<0.001
Female sex	785 (22)	213 (21)	0.356	289 (48)	192 (53)	0.198
Heart rate, bpm	80 ± 15	79 ± 19	0.366	76 ± 15	78 ± 16	0.062
SBP, mmHg	119 ± 20	116 ± 19	<0.001	134 ± 23	128 ± 22	<0.001
DBP, mmHg	73 ± 13	70 ± 13	<0.001	73 ± 13	71 ± 13	0.077
BMI, kg/m ²	25.1 ± 5.1	24.4 ± 5.0	<0.001	27.8 ± 6.2	26.3 ± 6.0	0.001
NYHA class III/IV	1118 (34)	342 (37)	0.046	117 (22)	84 (26)	0.266
NTproBNP*, pg/mL	2852 [1205,8040]	4110 [1915,7731]	<0.001	1804 [730,4690]	2808 [1417,5051]	0.081
Echocardiography						
LVEF, %	27 [22,33]	28 [22,34]	0.022	60 [55,65]	60 [55,66]	0.047
E/e'	22 ± 12	20 ± 10	0.011	17 ± 9	18 ± 7	0.41
LVMI, g/m ²	137 ± 47	139 ± 46	0.367	109 ± 38	109 ± 45	0.978
LAVI, mL/m ²	36 ± 18	55 ± 24	<0.001	31 ± 14	52 ± 22	<0.001
Medical history						
Ischaemic heart failure	1769 (53)	406 (42)	<0.001	203 (38)	101 (31)	0.049
Hypertension	1825 (52)	545 (54)	0.319	429 (72)	277 (76)	0.138
Diabetes	1572 (45)	384 (38)	<0.001	313 (52)	159 (44)	0.01
Chronic kidney disease	1113 (41)	443(50)	<0.001	249 (53)	168 (53)	0.895
Prior stroke	187 (5)	119 (12)	<0.001	37 (6)	47 (13)	<0.001
Peripheral arterial disease	110 (3)	46 (5)	0.03	13 (2)	5 (1)	0.8
Chronic respiratory disease	274 (8)	89 (9)	0.31	45 (8)	38 (10)	0.12
Smoking history	1576 (45)	506 (50)	0.004	141 (24)	90 (25)	0.669
Alcohol history	963 (27)	376 (37)	<0.001	84 (14)	73 (20)	0.013
KCCQ*						
Physical limitation score	75 (50–92)	71 (50–90)	0.08	83 (63–95)	75 (54–92)	0.06
Quality of life score	58 (33–75)	58 (33–75)	0.05	75 (50–83)	67 (42–83)	0.04
Social limitation score	69 (38–94)	58 (25–91)	<0.001	83 (58–100)	75 (50–100)	0.27
Total symptom score	75 (53–92)	75 (50–94)	0.54	81 (58–96)	78 (53–93)	0.08
Clinical summary score	72 (54–89)	71 (50–88)	0.21	80 (62–94)	74 (55–91)	0.01
Overall score	68 (47–84)	64 (44–83)	0.02	78 (59–91)	72 (53–88)	0.02
Medications						
ACE-I/ARB	2691 (78)	719 (72)	<0.001	367 (69)	202 (59)	0.004
Beta blocker	2665 (77)	795 (80)	0.076	357 (67)	247 (73)	0.077
MRA	2032 (59)	590 (59)	0.818	103 (19)	91 (27)	0.01
Digoxin	860 (25)	416 (42)	<0.001	11 (2)	74 (22)	<0.001
Diuretic	2852 (82)	851 (85)	0.033	373 (70)	278 (82)	<0.001

ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; KCCQ, Kansas City Cardiomyopathy questionnaire; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.

Comparison of baseline characteristics among patients with and without AF in HFrEF and HFpEF. Values expressed as mean \pm standard deviation or percentage (%). * values are expressed as median (lower quartile, upper quartile).

HFrEF (38%) ($P < 0.001$). Baseline characteristics of patients by in AF and sinus rhythm by HF type are shown in *Table 1*, and baseline characteristics of all HF patients stratified by ethnicity in *Table S1*. Patients with AF (compared with sinus rhythm) were older and more likely to have a history of prior stroke, higher NT-proBNP levels, and larger LA volumes but less likely to have diabetes and ischemic heart disease. Mean heart rate was similar between AF and sinus rhythm in both HFrEF and HFpEF, with similar beta blocker usage between AF and sinus rhythm but higher digoxin use in AF. Japanese/Korean had the largest LA size while Indians had the smallest in AF, regardless of HF type (*Table 2*). Among patients with HFrEF, 1956 (43%) had diabetes (mean duration 9.7 ± 8.1 years, 98% type 2 diabetes, 25% oral hypoglycemic agents, 8% insulin), while 452 (47%) patients with HFpEF had diabetes (mean duration 12.5 ± 8.9 years, 98% type 2 diabetes, 29% oral hypoglycemic agents, 11% insulin).

Prevalence of atrial fibrillation within Asia

The prevalence of AF by ethnicity and geographical region within Asia is shown in *Figure 1*. Compared with Chinese, Indians had lower prevalence of AF in both HFpEF (7% vs. 28%, $P < 0.001$) and HFrEF (17% vs. 42%, $P < 0.001$), while Japanese/Koreans had higher prevalence of AF in HFrEF (47% vs. 28%, $P < 0.001$). Significant ethnic differences were noted in the association with AF by HF type in multivariable models adjusted for demographics, clinical correlates, and medications (*Figure 2*). Ethnic differences persisted in sensitivity analyses after further adjustment for LAVI ($n = 1670$ in HFrEF, $n = 280$ in HFpEF) [Indian: adjusted odds ratio (AOR) in HFrEF 0.25, 95% CI 0.17–0.36, AOR in HFpEF 0.35, 95% CI 0.18–0.68; Japanese/Korean: AOR in HFrEF 3.94, 95% CI 2.81–5.54].

Only Chinese and Indians were represented in more than one geographical bloc, with striking geographical variations present in subgroup analyses. Among 1659 Indians, 141 (8%) had AF (16% Southeast Asia vs. 7% South Asia, $P < 0.001$). Southeast Asian Indians were three times as likely to have AF compared with South Asian Indians, even after adjusting for clinical covariates (AOR 3.01, 95% CI 1.60–

5.67), with no interaction by HF type ($p_{\text{interaction}} = 0.15$). Among 1837 Chinese, 577 (31%) had AF, with lower prevalence of AF in Southeast Asia than Northeast Asia (29% vs. 34%, respectively, $P = 0.03$). Southeast Asian Chinese were less likely to have AF compared with Northeast Asian Chinese with no interaction by HF type ($p_{\text{interaction}} = 0.50$), but this was attenuated after adjusting for differences in baseline characteristics (as above) (AOR 0.95, 95% CI 0.72–1.27).

Clinical correlates of atrial fibrillation by heart failure type

The clinical correlates of AF in HFrEF and HFpEF were similar across ethnicities (no significant interaction by ethnicity, *Figure 2*). Diabetes was consistently associated with lower odds of AF in both HFrEF (AOR 0.79, 95% CI 0.66–0.95) and HFpEF (AOR 0.58, 95% CI 0.39–0.84) in multivariable analyses. Adjusting for age, sex, ethnicity, and BMI, anti-diabetic medications were not associated with AF (*Table S2*). The association between diabetes and AF was modified by BMI in patients with HFrEF ($p_{\text{interaction}}$ in HFrEF = 0.001, $p_{\text{interaction}}$ in HFpEF = 0.27). Among obese (BMI ≥ 30 kg/m²) patients with HFrEF, diabetes was not associated with AF (OR 1.39, 95% CI 0.92–2.10); whereas in non-obese patients with HFrEF, diabetes was associated with lower risk of AF (OR 0.69, 95% CI 0.59–0.81).

Association of atrial fibrillation with quality of life

Patients with AF had poorer QoL based on KCCQ indices in both HFrEF and HFpEF, with lowest overall score in HFrEF (*Table 1*). Adjusted for demographics, clinical confounders and education, patients with AF had lower social limitation scores but similar overall summary scores without HF type interactions in all domains (*Table S3*). Ethnic variation was noted only for social limitation ($p_{\text{interaction}}$ for ethnicity = 0.009), such that Indians with AF had lower social limitation scores (adjusted β coefficient -12.4 , $P < 0.001$), a difference not observed in the other ethnicities.

Table 2 Comparison of LAVI by ethnicity

	Chinese	Indian	Malay	Japanese/Korean	Others	P value
HFrEF						
AF	56.8 \pm 22.1	39.2 \pm 19.9	39.6 \pm 20.7	63.3 \pm 26.9	47.5 \pm 17.8	<0.001
SR	44.8 \pm 17.0	28.1 \pm 16.6	36.2 \pm 16.7	44.2 \pm 17.4	36.1 \pm 16.9	<0.001
HFpEF						
AF	54.8 \pm 22.6	42.4 \pm 18.0	41.5 \pm 18.2	59.2 \pm 21.6	NA	0.02
SR	36.7 \pm 13.5	25.9 \pm 13.6	25.6 \pm 8.8	39.7 \pm 14.8	24.1 \pm 6.8	<0.001

Comparison of LAVI in patients with and without AF in HFrEF and HFpEF stratified by ethnicity.

AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume indexed by body surface area; SR, sinus rhythm.

Figure 1 Prevalence of atrial fibrillation by ethnicity and geographical region in within Asia. Prevalence of AF by ethnicity (upper panel) and geographical region (lower panel), classified by HFpEF (blue) and HFrEF (red). AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

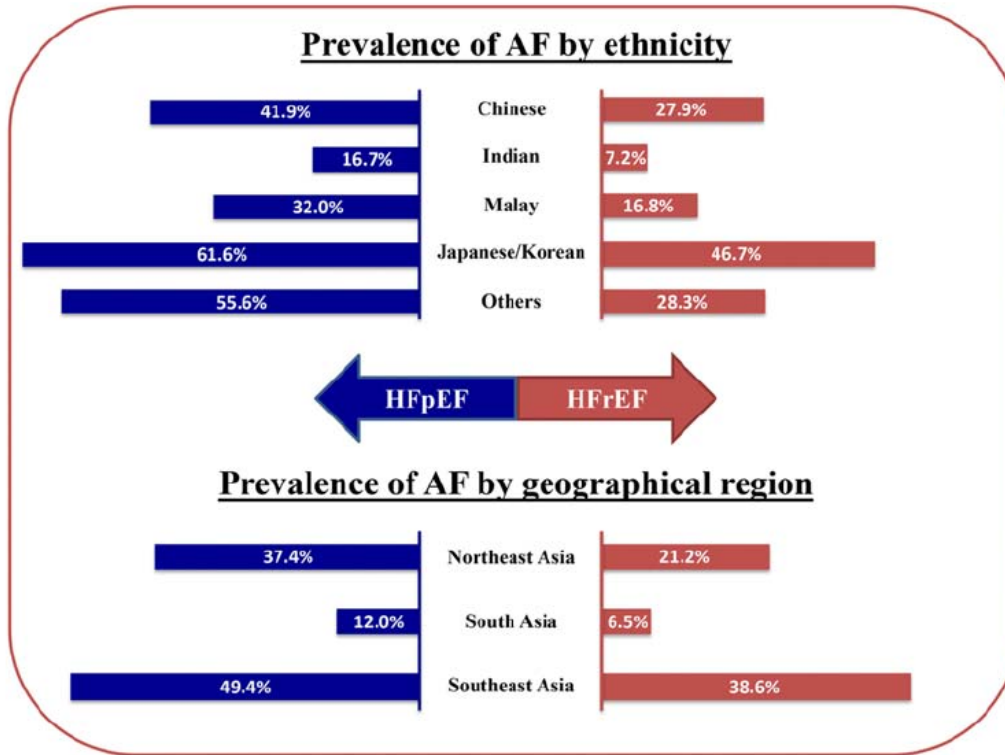
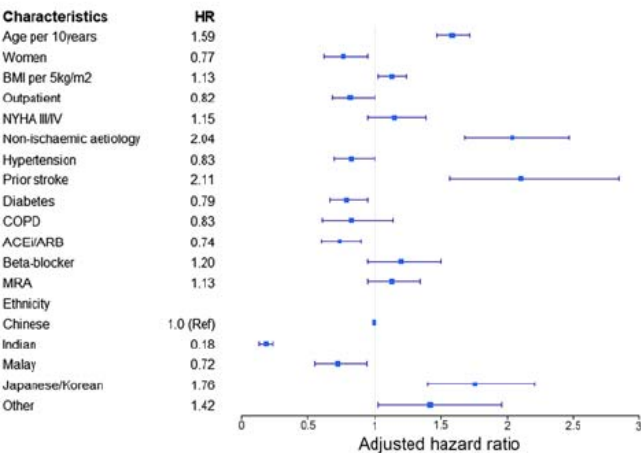
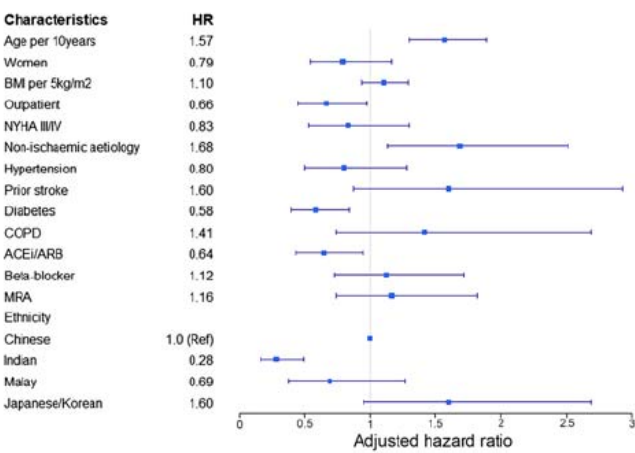


Figure 2 Association of clinical correlates with atrial fibrillation in (A) HFrEF and (B) HFpEF. Multivariable analysis of the association of clinical correlates including ethnicity (Chinese as reference ethnic race) with atrial fibrillation in (A) HFrEF and (B) HFpEF. ACE-I, angiotensin-converting enzyme inhibitor; AOR, adjusted odds ratio; ARB, angiotensin receptor-II blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association functional class; MRA, mineralocorticoid receptor antagonist.

A. HFrEF



B. HFpEF



Association of atrial fibrillation with outcomes

Over a follow-up period of 1 year, 982 (20%) patients either died or were hospitalized for HF (24% AF vs. 18% sinus rhythm, $P < 0.001$). AF was associated with increased primary outcome (OR 1.42, 95% CI 1.24–1.63), without interaction by HF type ($p_{\text{interaction}} = 0.39$). Similar associations were observed for all-cause mortality (12% AF vs. 9% sinus rhythm, $P < 0.001$) and HF hospitalizations (16% AF vs. 11% sinus rhythm, $P < 0.001$). In separate multivariable models, AF increased the risk of all-cause mortality (adjusted HR 1.61, 95% CI 1.27–2.06) and HF hospitalizations accounting for death as competing risk (adjusted HR 1.24, 95% CI 1.02–1.52), both without interaction by HF type ($p_{\text{interaction}} > 0.05$).

Although Kaplan–Meier survival curves by ethnicity appeared to show that the association of AF with poor survival was stronger in Chinese and Indians compared with Malays and Japanese/Koreans (Figure 3), formal ethnic interaction testing was non-significant ($p_{\text{interaction}} = 0.08$). These associations among Chinese and Indians persisted even after adjusting for age, sex, BMI, NYHA class, enrolment type, HF type, HF aetiology, diabetes, hypertension, stroke, and CKD but not was present in Malays, Japanese/Koreans, and indigenous Southeast Asians (Chinese: AHR 1.51, 95% CI 1.21–1.88; Indian: AHR 2.26, 95% CI 1.26–4.06; Malay: AHR 1.16, 95% CI 0.81–

1.65; Japanese/Korean: AHR 0.93, 95% CI 0.58–1.49; Others: AHR 1.44, 95% CI 0.60–3.50). In the total cohort of HF patients, AF independently increased the risk of the composite outcome of 1 year all-cause mortality or HF hospitalisation in multiple models of multivariable adjustments (Table 3).

Discussion

The prospective multinational ASIAN-HF study provides novel findings on the ethnic differences in prevalence of AF among patients with HF recruited across Asia using identical protocols and extends upon previous studies in several important ways: (i) it is the first multinational study on ethnic differences and clinical correlates of AF in Asia; (ii) by having large numbers of adjudicated outcomes and comprehensive QoL data; and (iii) having good representation of different ethnicities in Asia from countries at divergent economic levels. Indians had the lowest prevalence of AF regardless of HF type, while Japanese/Korean with HFrEF had the highest prevalence of AF. Interestingly, the association with AF differed according to geographical locations among the same ethnicity, with Southeast Asian Indians having higher odds of AF compared with Northeast Asian Indians. Clinical

Figure 3 Kaplan–Meier survival curves of patients with AF vs. sinus rhythm by ethnicity. Kaplan–Meier survival curves of the association of AF with primary composite event of HF hospitalisation and all-cause mortality among Chinese, Indians, Malays and Japanese/Koreans with HF, with separation of survival curves among Chinese and Indians. AF, atrial fibrillation; HF, heart failure.

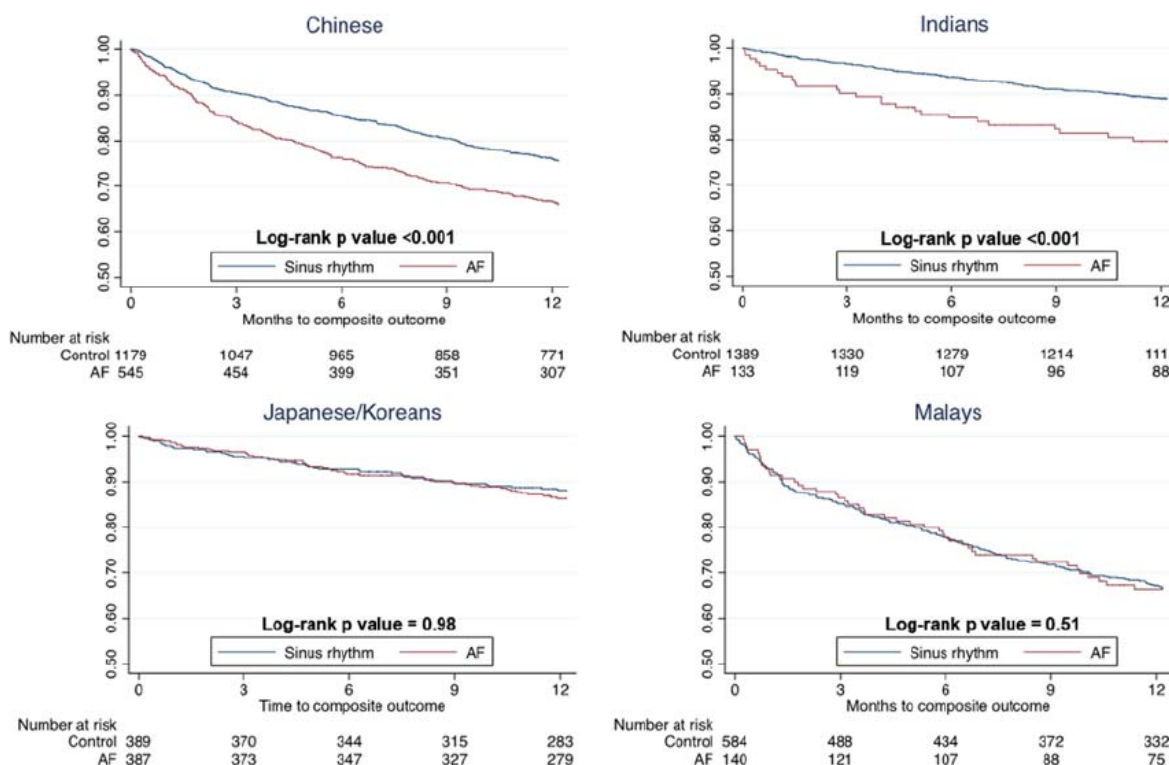


Table 3 Association of AF with 1 year primary composite endpoint of HF hospitalisation or all-cause mortality

	Hazard ratio	95% CI	P value
Crude AF	1.42	1.24–1.63	<0.001
AF + Age	1.34	1.16–1.54	<0.001
Model A	1.31	1.13–1.52	<0.001
Model B	1.38	1.18–1.63	<0.001

Association of AF with primary composite endpoint of HF hospitalisation or all-cause mortality in multivariable adjustment models.

Model A: adjusted for age, sex, BMI, NYHA, ethnicity, and enrolment type.

Model B: Model A + HF type, HF aetiology, hypertension, diabetes, stroke, chronic kidney disease.

AF, atrial fibrillation; BMI, body mass index; HF, heart failure; NYHA, New York Heart Association functional class

correlates and adverse outcomes associated with AF were similar across ethnicities.

Ethnic variations among Asian-heart failure patients

Although the SHOP-PEOPLE study previously reported a lower prevalence of AF among Asian patients with HF, it was not powered to detect differences between the three major ethnic races within Singapore and significant heterogeneity exists within Asian ethnicities.⁵ The ASIAN-HF study offers a unique opportunity for ethnic and interregional comparisons among a large contemporary cohort of Asian patients recruited simultaneously across multiple Asian countries using identical study procedures. We report a prevalence of 25% of AF in HF within Asia, consistent with prior observations of 16–42% among Asian HF patients.^{11,12} Additionally, we found ethnic differences in the prevalence of AF within Asia by HF type. In HFrEF, Japanese/Korean patients had the highest prevalence of AF, while Indians had the lowest prevalence of AF in both HFpEF and HFrEF. The significance of ethnicity was previously demonstrated among Asian women in the Women's Health Initiative,¹³ while South Asians in the United Kingdom had lower AF prevalence, attributed to inherent genetic differences that render atria morphologically and physiologically distinct.^{6,14} Ethnic variations in our study were independent of traditional AF risk factors. Furthermore, although ethnic differences in LA size may precede AF development, ethnic variations notably among Japanese/Koreans and Indians in AF prevalence persisted in sensitivity analyses after adjustment for LAVI, highlighting contributory roles of factors that remain unaccounted for. The development of AF is often multifactorial and the role of 'nature versus nurture' remains of great interest. Although non-shared environmental factors play a larger contributory role, genetic and shared environmental factors also participate in the pathogenesis of AF.⁷ An

interesting observation from our study was the differential AF associations among Indians in geographically separate locations. Local dietary habits, living conditions, and levels of physical activity may differ vastly in different regions of Asia. Singapore is an advanced economy with 'westernized' lifestyle, whereas the World Health Organization classifies India as a lower income region. The adoption of the 'western' lifestyle may explain the tripled odds of AF among Southeast Asian Indians (i.e. Singapore, Malaysia) compared with South Asian Indians (i.e. India). Indeed, the RACE-3 study highlighted the significance of lifestyle factors on AF, with exercise and dietary restrictions complementing HF medications in AF reduction.¹⁵ Nonetheless, the lower prevalence of AF among Indians is consistent with previous studies^{6,14} and suggests an intrinsic effect of Indian ethnicity, compared with other ethnicities, on AF. Ethnic variations in AF are thus likely a result of complex interactions between genetic and environmental factors that are population specific, suggesting the need for targeted therapy among different populations.

Diabetes-atrial fibrillation paradox

Although diabetes is a well-recognized risk factor for AF, the paradoxically protective effect of diabetes on AF was reported in Swedish-HF, SHOP-PEOPLE, and GWTG-HF.^{1,5,16} We now extend this paradoxical association for the first time to a larger cohort across Asia in both HFrEF and HFpEF. The exact mechanisms remain unknown, although we have previously thought it unlikely to be an effect of collider bias.¹⁷ Separately, diabetic medications had been reported to decrease the risk of AF. Modulation of electrical and mechanical properties of pulmonary veins and atria by dipeptidyl peptidase-4 inhibitors, inhibition of inflammation and oxidation by metformin and reduction of proarrhythmic substrates via inhibition of ATP-sensitive potassium channels by glibenclamide and tolbutamide have been suggested to confer protective benefits against AF.^{18–20} However, antidiabetic medications did not exhibit the same relationship with AF after adjusting for patient demographics in our study. The absence of treatment effect in our study is likely because of different cardiac substrates, with HF patients more likely to have undergone structural and electrical remodelling, while prior studies were in animals or populations with largely structurally normal hearts. Biological plausibility for the diabetes-AF paradox remains unproven, but previous studies have shown diabetes to be associated with inward remodelling effects in the paradoxical protection against aortic aneurysms, smaller LV volumes and more concentric LV remodelling.^{21–24} The protection from outward remodelling has been attributed to advanced glycation end-product (AGE) cross links, with AGE cross link breaker treatment leading to LV dilatation.²⁵ Given our previous finding of smaller LAVI in diabetes

regardless of AF or HF subtype,⁵ diabetic protection against atrial outward remodelling may plausibly confer a lower risk of AF. In non-HF cohorts, BMI was acknowledged as a residual confounding factor in the increased risk of AF with diabetes.²⁶ An increased association with AF was found among obese patients but absent among patients with normal weight.²⁷ Similarly, two Japanese studies, with mean BMI within normal ranges (22–25 kg/m²) did not demonstrate an association between diabetes and AF.^{28,29} When stratified by BMI, the diabetes-AF paradox was only observed in non-obese patients with HFrEF, and not in obese patients in whom the obesity-associated higher odds of AF may have masked any diabetes-related lower odds of AF. The exact mechanisms by which obesity and diabetes interact in predisposing to AF remains unknown, although interestingly, the Look AHEAD trial did not find a reduction in AF among diabetic patients even with modest weight reduction.³⁰ It should be noted however, that the mean BMI in Look AHEAD (36 kg/m²) was much higher than in ASIAN-HF (25 kg/m²), and the modest weight loss of 6% in Look AHEAD might have been insufficient to reduce the risk of AF.

Association of atrial fibrillation with outcomes

AF portends a poorer prognosis in HF. We found a direct association of AF with death or HF hospitalisation regardless of HF type, consistent with the Swedish-HF registry.¹ Data on ethnic differences in outcomes with AF in the context of HF are conflicting. Higher in-hospital mortality in black compared with white, Hispanic, and Asian-American HF patients with AF were noted,³ but ethnic differences were not observed between black and white patients in the GWTH-HF registry⁴ or Asian and white patients in the Asia-Pacific SHOP-PEOPLE study.⁵ Although ethnic interactions with primary outcome were not statistically significant, the distinct separation in Kaplan–Meier survival curves by AF among Chinese and Indians persisted even after adjusting for demographics and clinical co-morbidities. Exact mechanisms underlying these observations are uncertain and deserve further study.

Limitations

We acknowledge the potential of selection bias from site selection and variations in patient willingness to participate in a prospective registry. Site selection in ASIAN-HF was based on the size and geographical location within the country, patient population, and availability of expertise in echocardiography. Efforts were made to ensure protocol standardisation and adherence, including region-specific language translations, on-site investigator training and regular monitoring, and centralized database management in order to maintain quality

data and minimize missing data. Ethnicity was self-reported, with the potential for misclassification. The number of indigenous Southeast Asian patients with HFpEF was too small to allow for meaningful comparisons. We recognize the differences in healthcare systems and cultural barriers to healthcare access within Asia, which may potentially affect the AF and HF burden in our study. Duration of AF and the incidence of AF during the course of follow-up were unavailable. Analyses of AF prevalence were cross-sectional and do not allow ascertainment of temporal relationships between AF and other clinical factors. Moreover, patients with asymptomatic paroxysmal AF may have been undetected, although the inclusion of these patients will unlikely attenuate the strong relationships with AF seen in our study.

Conclusions

Among patients with HF across Asia, clinical correlates and adverse outcomes associated with AF are similar across ethnicities; however, there are striking ethnic variations in the prevalence of AF that are not accounted for by known risk factors.

Acknowledgements

The contribution of all the site investigators and clinical co-ordinators are duly acknowledged.

Conflict of interest

CSPL is supported by a Clinician Scientist Award from the National Medical Research Council Singapore. CSPL has received research support from Boston Scientific, Medtronic, and Vifor Pharma, and has consulted for Bayer, Novartis, Takeda, Merck, Astra Zeneca, Janssen Research & Development, LLC and Menarini. She has served on the Clinical Endpoint Committee for DC Devices. AMR has received research support from Boston Scientific, Bayer, Astra Zeneca, Medtronic, Roche Diagnostics, Abbott Laboratories, Thermo Fisher, Critical Diagnostics and has consulted for Bayer, Novartis, Merck, Astra Zeneca, Roche Diagnostics. The other authors have no conflict of interests to declare.

Funding

The ASIAN-HF study is supported by grants from Boston Scientific Corporation (Investigator Sponsored Research Program), National Medical Research Council Singapore, A*STAR (Agency for Science, Technology and Research)

Biomedical Research Council ATTRaCT program and Bayer Corporation.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of all heart failure patients stratified by ethnicity.

Table S2. Association of anti-diabetic drugs with AF in HF (n = 2428)

Table S3. Adjusted mean KCCQ domains scores

References

- Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail* 2017; **5**: 565–574.
- Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016; **203**: 660–666.
- Bhatia S, Qazi M, Erande A, Shah K, Amin A, Patel P, Malik S. Racial differences in the prevalence and outcomes of atrial fibrillation in patients hospitalized with heart failure. *Am J Cardiol* 2016; **117**: 1468–1473.
- Thomas KL, Piccini JP, Liang L, Fonarow GC, Yancy CW, Peterson ED, Hernandez AF. Get with the guidelines steering committee and hospitals racial differences in the prevalence and outcomes of atrial fibrillation among patients hospitalized with heart failure. *J Am Heart Assoc* 2013; **2**: e000200.
- Tan ESJ, Tay WT, Teng TK, Sim D, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Poppe K, Lund M, Devlin G, Troughton RW, Ling LH, Richards AM, Doughty RN, Lam CSP. Ethnic differences in atrial fibrillation in patients with heart failure from Asia-Pacific. *Heart* 2019; **105**: 842–847.
- Gillott RG, Willan K, Kain K, Sivananthan UM, Tayebjee MH. South Asian ethnicity is associated with a lower prevalence of atrial fibrillation despite greater prevalence of established risk factors: a population-based study in Bradford Metropolitan District. *Europace* 2017; **19**: 356–363.
- Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Huang LH, Zhang W, Doherty M, Wen MS, Kuo CT, Yeh YH. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a population-based family cohort study. *JAMA Cardiol* 2017; **2**: 863–870.
- Lam CS, Teng TK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto BB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. *Eur Heart J* 2016; **37**: 3141–3153.
- Tromp J, Teng TH, Tay WT, Hung CL, Narasimhan C, Shimizu W, Park SW, Liew HB, Ngarmukos T, Reyes EB, Siswanto BB, Yu CM, Zhang S, Yap J, MacDonald M, Ling LH, Leineweber K, Richards AM, Zile MR, Anand IS, Lam CSP, ASIAN-HF Investigators. Heart failure with preserved ejection fraction in Asia. *Eur J Heart Fail* 2019; **21**: 23–36.
- Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000; **35**: 1245–1255.
- Guo Y, Lip GY, Banerjee A. Heart failure in East Asia. *Curr Cardiol Rev* 2013; **9**: 112–122.
- Reyes EB, Ha JW, Firdaus I, Ghazi AM, Phrommintikul A, Sim D, Vu QN, Siu CW, Yin WH, Cowie MR. Heart failure across Asia: same healthcare burden but differences in organization of care. *Int J Cardiol* 2016; **223**: 163–167.
- Rodriguez F, Stefanick ML, Greenland P, Soliman EZ, Manson JE, Parikh N, Martin LW, Larson JC, Hlatky M, Nassir R, Cené CW, Rodriguez BL, Albert C, Perez MV. Racial and ethnic differences in atrial fibrillation risk factors and predictors in women: findings from the Women's Health Initiative. *Am Heart J* 2016; **176**: 70–77.
- O'Neill J, Tayebjee MH. Why are South Asians seemingly protected against the development of atrial fibrillation? A review of current evidence. *Trends Cardiovasc Med* 2017; **27**: 249–257.
- Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brügemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, Van Veldhuisen DJ, Crijns HJGM, Van Gelder IC, RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018; **39**: 2987–2996.
- Echouffo-Tcheugui JB, Xu H, DeVore AD, Schulte PJ, Butler J, Yancy CW, Bhatt DL, Hernandez AF, Heidenreich PA, Fonarow GC. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: findings from get with the guidelines-heart failure registry. *Am Heart J* 2016; **182**: 9–20.
- Tan ESJ, Tay WT, Teng TK, Richards AM, Doughty RN, Lam CSP. The diabetes-atrial fibrillation paradox. *Heart* 2019; **105**: 893.
- Chang CY, Yeh YH, Chan YH, Liu JR, Chang SH, Lee HF, Wu LS, Yen KC, Kuo CT, See LC. Dipeptidyl peptidase-4 inhibitor decreases the risk of atrial fibrillation in patients with type 2 diabetes: a nationwide cohort study in Taiwan. *Cardiovasc Diabetol* 2017; **16**: 159.
- Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, Wen MS, Chen WJ, Yeh YH, See LC. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol* 2014; **13**: 123.
- Kim SJ, Zhang H, Khaliulini I, Choisy SC, Bond R, Lin H, El Haou S, Milnes JT, Hancox JC, Suleiman MS, James AF. Activation of glibenclamide-sensitive ATP-sensitive K⁺ channels during β -adrenergically induced metabolic stress produces a substrate for atrial tachyarrhythmia. *Circ Arrhythm Electrophysiol* 2012; **5**: 1184–1192.
- Raffort J, Lareyre F, Clément M, Hassen-Khodja R, Chinetti G, Mallat Z. Diabetes and aortic aneurysm: current state of the art. *Cardiovasc Res* 2018; **114**: 1702–1713.
- MacDonald MR, She L, Doenst T, Binkley PF, Rouleau JL, Tan RS, Lee KL, Miller AB, Sopko G, Szalewska D, Waclawiw MA, Dabrowski R, Castelvichio S, Adlbrecht C, Michler RE, Oh JK, Velazquez EJ, Petrie MC. Clinical characteristics and outcomes of patients with and without diabetes in the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *Eur J Heart Fail* 2015; **17**: 725–734.

23. Solomon SD, St John Sutton M, Lamas GA, Plappert T, Rouleau JL, Skali H, Moyé L, Braunwald E, Pfeffer MA, Survival And Ventricular Enlargement (SAVE) Investigators. Ventricular remodeling does not accompany the development of heart failure in diabetic patients after myocardial infarction. *Circulation* 2002; **106**: 1251–1255.
24. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, Køber L, McKelvie RS, Zile MR, Anand IS, Komajda M, Gottdiener JS, Carson PE, McMurray JJ. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation* 2017; **135**: 724–735.
25. Willemssen S, Hartog JW, Hummel YM, Posma JL, van Wijk LM, van Veldhuisen DJ, Voors AA. Effects of alagebrium, an advanced glycation end-product breaker, in patients with chronic heart failure: study design and baseline characteristics of the BENEFICIAL trial. *Eur J Heart Fail* 2010; **12**: 294–300.
26. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications* 2018; **32**: 501–511.
27. Schoen T, Pradhan AD, Albert CM, Conen D. Type 2 diabetes mellitus and risk of incident atrial fibrillation in women. *J Am Coll Cardiol* 2012; **60**: 1421–1428.
28. Suzuki H, Ohira T, Takeishi Y, Hosoya M, Yasumura S, Satoh H, Kawasaki Y, Takahashi A, Sakai A, Ohtsuru A, Kobashi G, Ozasa K, Yamashita S, Kamiya K, Abe M, Fukushima Health Management Survey Group. Increased prevalence of atrial fibrillation after the Great East Japan Earthquake: results from the Fukushima Health Management Survey. *Int J Cardiol* 2015; **198**: 102–105.
29. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kusano K, Miyamoto Y. Development of a basic risk score for incident atrial fibrillation in a Japanese general population—the Suita study. *Circ J* 2017; **81**: 1580–1588.
30. Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson KC, Lewis CE, Vetter M, Mantzoros CS, Jeffery RW, Solomon EZ, Look AHEAD Research Group. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: the Look AHEAD randomized trial. *Am Heart J* 2015; **170**: 770–777.

Appendix: The ASIAN-HF executive committee

- Professor A. Mark Richards (as Chairman), Cardiovascular Research Institute, National University of Singapore, Singapore. Email: mdcarthu@nus.edu.sg
- Professor Carolyn S.P. Lam (as Principal Investigator), National Heart Centre Singapore, Duke-NUS Medical School, Singapore. Email: carolyn.lam@duke-nus.edu.sg
- Professor Inder Anand (as Director, Publications Committee), University of Minnesota Medical School, VA Medical Center Minneapolis and San Diego, United States of America. Email: anand001@umn.edu
- Dr Chung-Lieh Hung, Mackay Memorial Hospital, Taipei, Taiwan. Email: jotaro3791@gmail.com
- Associate Professor Lieng Hsi Ling (as Director, Echo Core Laboratory), Cardiovascular Research Institute, National University of Singapore, Singapore. Email: lieng_hsi_ling@nuhs.edu.sg
- Dr Hiong Bang Liew, Queen Elizabeth II Hospital, Clinical Research Center, Sabah, Malaysia. Email: hbliew22@gmail.com
- Dr Calambur Narasimhan, Care Hospital, Hyderabad, India. Email: calambur@hotmail.com
- Dr Tachapong Ngarmukos, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. Email: tachaponis.nga@mahidol.ac.th
- Dr Sang Weon Park, SeJong General Hospital, Seoul, South Korea. Email: swparkmd@gmail.com

- Dr Eugenio Reyes, Manila Doctors Hospital, Manila, Philippines. Email: eugenereyes@yahoo.com
- Professor Bambang B. Siswanto, National Cardiovascular Center Universitas Indonesia, Jakarta, Indonesia. Email: bambbs@gmail.com
- Professor Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan. Email: wshimizu@nms.ac.jp
- Professor Shu Zhang, Fuwai Cardiovascular Hospital, Beijing, People's Republic of China. Email: zsfuwai@vip.163.com

Country and site investigators

China

Fuwai Hospital: **Shu Zhang** (Country PI), Xiaohan Fan, Keping Chen. Ruijin Hospital, Shanghai Jiaotong university: Liqun Wu, Yucai Xie, Qi Jin, Tianyou Ling. The First Affiliated Hospital With Nanjing Medical University: Xinli Li, Fang Zhou, Yanli Zhou, Dongjie Xu, Haifeng Zhang. Zhongshan Hospital Fudan University: Yangang Su, Xueying Chen, Shengmei Qin, Jingfeng Wang, Xue Gong, Zhaodi Wu.

Hong Kong

The Chinese University of Hong Kong: **Cheuk Man Yu** (Country PI).

India

CARE Hospital: **Calambur Narasimhan** (Country PI), B K S Sastry, Arun Gopi, K Raghu, C Sridevi, Daljeet Kaur. Care Institute of Medical Sciences: Ajay Naik, Keyur Parikh, Anish Chandarana, Urmil Shah, Milan Chag, Hemang Baxi, Satya Gupta, Jyoti Bhatia, Vaishali Khakhhar, Vineet Sankhla, Tejas

Patel, Vipul Kapoor. Hero Dayanand Medical College Heart Institute: Gurpreet Singh Wander, Rohit Tandon. Medanta-The Medicity: Vijay Chopra, Manoj Kumar, Hatinder Jeet Singh Sethi, Rashmi Verma, Sanjay Mittal. Sir Ganga Ram Hospital: Jitendra Sawhney, Manish Kr. Sharma. Westfort Hi-Tech Hospital Ltd: Mohanan Padinhare Purayil.

Indonesia

Rumah Sakit Jantung dan Pembuluh Darah Harapan Kita: **Bambang Budi Siswanto** (Country PI). RS Dr Hasan Sadikin: Pintoko Tedjokusumo, Erwan Martanto, Erwinanto. R S Khusus Jantung Binawaluya: Muhammad Munawar, Jimmy Agung Pambudi. RS Siloam Karawaci: Antonia Lukito, Ingrid Pardede, Alvin Thengker, Vito Damay, Siska Suridanda Danny, Rarsari Surarso.

Japan

Nippon Medical School: **Wataru Shimizu** (Country PI), National Cerebral and Cardiovascular Center: Takashi Noda, Ikutaro Nakajima, Mitsuru Wada, Kohei Ishibashi. Kinki University Hospital Cardiovascular Center: Takashi Kurita, Ryoubun Yasuoka. Nippon Medical School Hospital: Kuniya Asai, Kohji Murai, Yoshiaki Kubota, Yuki Izumi. Toho University Omori Medical Center: Takanori Ikeda, Shinji Hisatake, Takayuki Kabuki, Shunsuke Kiuchi, Tokyo Women's Medical University: Nobuhisa Hagiwara, Atsushi Suzuki, Dr. Tsuyoshi Suzuki.

Korea

SeJong General Hospital: **Sang-Weon Park** (Country PI), Suk Keun Hong, SookJin Lee, Lim Dal Soo, Dong-Hyeok Kim. Korea University Anam Hospital: Jaemin Shim, Seong-Mi Park, Seung-Young Roh, Young Hoon Kim, Mina Kim, Jong-Il Choi. Korea University Guro Hospital: Jin Oh Na, Seung Woon Rha, Hong Seog Seo, Dong Joo Oh, Chang Gyu Park, Eung Ju Kim, Sunki Lee,

Severance Hospital, Yonsei University Health System: Boyoung Joung, Jae-Sun Uhm, Moon Hyoung Lee, In-Jeong Cho, Hui-Nam Park. Chonnam National University Hospital: Hyung-Wook Park, Jeong-Gwan Cho, Namsik Yoon, KiHong Lee, Kye Hun Kim. Korea University Ansan Hospital: Seong Hwan Kim.

Malaysia

Hospital Queen Elizabeth II: **Houng Bang Liew** (Country PI), Sahrin Saharudin, Boon Cong Beh, Yu Wei Lee, Chia How Yen, Mohd Khairi Othman, Amie-Anne Augustine, Mohd Hariz Mohd Asnawi, Roberto Angelo Mojolou, You Zhuan Tan, Aida Nurbaini Arbain, Chii Koh Wong. Institut Jantung Negara: Razali Omar, Azmee Mohd Ghazi, Surinder Kaur Khelae, David S.P. Chew, Lok Bin Yap, Azlan Hussin, Zulkeflee Muhammad,

Mohd. Ghazi Azmee. University Malaya Medical Centre: Imran Zainal Abidin, Ahmad Syadi Bin Mahmood Zhudi, Nor Ashikin Md Sari, Ganiga Srinivasaiah Sridhar, Ahmad Syadi Mahmood Zuhdi. Muhammad Dzafir Ismail. Sarawak General Hospital Heart Centre: Tiong Kiam Ong, Yee Ling Cham, Ning Zan Khiew, Asri Bin Said, Alan Yean Yip Fong, Nor Hanim Mohd Amin, Keong Chua Seng, Sian Kong Tan, Kuan Leong Yew.

Philippines

Manila Doctors Hospital: **Eugenio Reyes** (Country PI), Jones Santos, Allan Lim. Makati Medical Center: Raul Lapitan, Ryan Andal, Philippine Heart Center: Eleanor Lopez.

Singapore

National Heart Centre Singapore: **Carolyn S.P. Lam** (Country PI), Kheng Leng David Sim, Boon Yew Tan, Choon Pin Lim, Louis L.Y. Teo, Laura L.H. Chan. National University Heart Centre: Lieng Hsi Ling, Ping Chai, Ching Chiew Raymond Wong, Kian Keong Poh, Tan Tock Seng Hospital: Poh Shuan Daniel Yeo, Evelyn M. Lee, Seet Yong Loh, Min Er Ching, Deanna Z. L. Khoo, Min Sen Yew, Wenjie Huang. Changi General Hospital-Parent: Kui Toh Gerard Leong, Jia Hao Jason See, Yaozong Benji Lim, Svenszeat Tan, Colin Yeo, Siang Chew Chai. Singapore General Hospital-Parent: Fazlur Rehman Jaufeerally, Haresh Tulsidas, Than Aung. Khoo Teck Puat Hospital: Hean Yee Ong, Lee Fong Ling, Dinna Kar Nee Soon.

Taiwan

Mackay Memorial Hospital, Taipei, Taiwan: **Chung-Lieh Hung** (Country PI), Hung-I Yeh, Jen-Yuan Kuo, Chih-Hsuan Yen. National Taiwan University Hospital: Juey-Jen Hwang, Kuo-Liong Chien, Ta-Chen Su, Lian-Yu Lin, Jyh-Ming Juang, Yen-Hung Lin, Fu-Tien Chiang, Jiunn-Lee Lin, Yi-Lwun Ho, Chii-Ming Lee, Po-Chih Lin, Chi-Sheng Hung, Sheng-Nan Chang, Jou-Wei Lin, Chih-Neng Hsu. Taipei Veterans General Hospital: Wen-Chung Yu, Tze-Fan Chao, Shih-Hsien Sung, Kang-Ling Wang, Hsin-Bang Leu, Yenn-Jiang Lin, Shih-Lin Chang, Po-Hsun Huang, Li-Wei Lo, Cheng-Hsueh Wu. China Medical University Hospital: Hsin-Yueh Liang, Shih-Sheng Chang, Lien-Cheng Hsiao, Yu-Chen Wang, Chiung-Ray Lu, Hung-Pin Wu, Yen-Nien Lin, Ke-Wei Chen, Ping-Han Lo, Chung-Ho Hsu, Li-Chuan Hsieh.

Thailand

Ramathibodi Hospital: **Tachapong Ngarmukos** (Country PI), Mann Chandavimol, Teerapat Yingchoncharoen, Prasart Laothavorn. Phramongkutklao Hospital: Waraporn Tiyanon. Maharaj Nakorn Chiang Mai Hospital: Wanwarang Wongcharoen, Arintaya Phrommintikul.

